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<b>(54) Title:</b> FAST-DISSOLVING COMESTIBLE UNITS FORMED UNDER HIGH-SPEED/HIGH-PRESSURE CONDITIONS		
<b>(57) Abstract</b>  The invention relates to compositions useful for making tablets which can be formed using conventional tableting machines and which disintegrate rapidly in the mouth with optional chewing. The compositions typically include shearform matrices which have been recrystallized using crystallization promoters.		

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**FAST-DISSOLVING COMESTIBLE UNITS  
FORMED UNDER HIGH-SPEED/HIGH-PRESSURE CONDITIONS**

5           This is a continuation-in-part of U.S. SN. 08/915,067, filed August 20, 1997.

**FIELD OF THE INVENTION**

          The invention deals with compositions having enhanced cohesive and self-binding properties which permit tableting without added glycerine. Tablets made herewith disintegrate rapidly when placed in the mouth, especially when chewed.

10          **RELATED APPLICATIONS**

          This invention is related to U. S. SN. 08/915,068, filed August 20, 1997; U. S. Provisional filing SN. 60/056,617, filed August 20, 1997; and U. S. SN. 08/914,972, also filed August 20, 1997. Their disclosures are incorporated herein by reference.

**BACKGROUND OF THE INVENTION**

15           Glycerine, a tableting additive, has been used for its ability to lend stickiness to tablet formulations. Some stickiness is desirable, serving to provide cohesion to hold the tablet ingredients together during compression. However, in certain situations, the use of glycerine can produce too much stickiness, resulting in the formulations clumping or sticking in various machine parts before and during tableting. Self-binding, readily  
20          flowable compositions containing no glycerine have been unknown to the art.

          One method for addressing the need for self-binding flowable formulations was the production of shearform matrices or flosses. These matrices result when using certain processing techniques, such as the following:

          U. S. Patent 5,587,172, incorporated herein by reference, discusses the use of flash  
25          heat techniques to produce sucrose-containing shearform flosses, which are then processed to yield quick-dissolving tablets.

          The use of shearform matrices for forming comestible units is described in WO95/34290 (published December 21, 1995) from co-assigned PCT application No. PCT/US95/07144, filed June 6, 1995. This case discloses a quick dissolving tablet which  
30          is formed by: (1) using flash-flow technology to provide a shearform matrix; (2)

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combining the partially recrystallized shearform matrix with an additive to form flowable, compactible particulate blends; and (3) compacting the blends at relatively low pressures to form comestible units, such as tablets.

Additionally, PCT publication WO 95/34293 (published December 21, 1995)  
5 from co-assigned PCT Application No. PCT/US95/07194, filed June 6, 1995, discloses a process and apparatus for making rapidly dissolving dosage units by flash-flow processing. In this PCT application, a shearform matrix is formed by the flash-flow process, the shearform matrix is combined with an additive, and the matrix is molded to make a unit dosage form. Tamping may be used to compact the dosage form and increase  
10 its integrity.

While the use of shearform matrices is an advance in the art, there still exists a need for non-sticking tabletable compositions which, when molded, yield optionally chewable fast-dissolving dosage units. This invention addresses that need.

#### SUMMARY OF THE INVENTION

15 The invention provides compositions and dosage units having improved properties and methods of making them.

Co-owned U. S. Patent Application Serial No.08/915,068, filed August 20, 1997, describes tablet formulations derived from saccharide-based carriers in which the use of a unique combination of feedstock ingredients yields self-binding, flowable matrices and  
20 tablet compositions. This combination--which employs a blend of sugar alcohols, *i.e.*, sorbitol and xylitol--is superior to glycerine in providing cohesive properties and flowability.

Applicants have discovered that tablet compositions derived from hygroscopic matrices containing these sugar alcohols are useful--in the presence of tableting aids and  
25 crystallization promoters--in both high- and low-pressure tableting processes. Tablets therefrom rapidly dissolve when placed in the mouth, generally in less than 30 seconds, especially when chewed.

The tablet compositions of the invention are based on matrices which comprise at least one sugar alcohol, which matrices fall into one of the following groups:

30 One group--called "single floss" or "unifloss" systems--is exemplified by a

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shearform matrix, or floss, containing a carrier and two or more sugar alcohols, one of which is xylitol.

A second group—termed “dual floss”— is exemplified by (I) a first shearform carrier matrix (the “base floss”) comprising a carrier and at least one sugar alcohol,  
5 generally sorbitol; and (II) a second shearform binder matrix (the “binder floss”) comprising a carrier and xylitol.

Actives and other conventional tablet ingredients can be added, in suitable amounts, to the compositions of the present invention during the production of the matrices and/or after the matrices are collected and chopped, but before tableting.

## 10 DETAILED DESCRIPTION OF THE INVENTION

Unless otherwise stated, the parts and percentages used in the specification are weight percentages, based upon total composition weight. All disclosures referred to  
herein are hereby incorporated by reference.

The terms “matrix” and “floss” are used interchangeably.

15 Applicants have found that by using a combination of certain ingredients and process steps, tablets that dissolve in the mouth, with optional chewing, can be produced using conventional tableting equipment.

In addition, even though pressures of about 500 psi to about 10,000 psi or higher can be used on the inventive compositions, the dissolution time, in the mouth, for tablets  
20 made from this composition is in the range of from about 3 seconds to about 30 seconds. Prior art compositions required the use of specialized, low-pressure (less than 1000 psi) tableting equipment.

Additionally, it is now possible to prepare a partially crystalline tabletable composition, containing an active agent, with sufficient “flow” characteristics and  
25 properties to enable one to transport the composition to and through conventional tableting equipment. This composition can then be compacted under a wide range of tableting conditions.

The preparation of flosses suitable for use in the present invention is disclosed in co-assigned patent publications WO 95/34290 and WO 95/34293, both incorporated  
30 herein by reference. Preferably, the floss is a “shearform matrix” produced by subjecting

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a feedstock which contains a sugar carrier to flash-heat processing.

In the flash-heat process, the feedstock is simultaneously subjected to centrifugal force and to a temperature gradient which raises the temperature of the mass to create an internal flow condition which permits part of it to move with respect to the rest of the mass. The flowing mass exits through openings provided in the perimeter of a spinning head. The temperature gradient is supplied using heaters or other means which cause the mass temperature to rise. Centrifugal force in the spinning head flings the internally flowing mass outwardly, so that it reforms as discrete fibers with changed structures.

One apparatus which produces suitable conditions is a modified floss making machine, such as that described in

U. S. Patent Application Serial No. 08/854,344, filed on May 12, 1997.

Spinning is typically conducted at temperatures and speeds of about 150° C to 250°C and 3,000 to 5,000 rpm, respectively. Suitable spinner heads include that disclosed in U. S. Patent 5,458,823, assigned to Applicants' assignee.

Other apparatuses and processes which provide similar forces and temperature gradient conditions can be used.

The matrices used herein include, as feedstock ingredients, carrier materials, which carriers comprise at least one ingredient selected from materials which are capable of undergoing the physical and/or chemical changes associated with flash heat processing. Useful carriers include carbohydrates which become free-form particulates when flash heat processed. Saccharide-based carriers, including saccharides (*i.e.*, sugars), polysaccharides and mixtures thereof can be also used.

The feedstocks used in the invention can include carriers chosen from various classes of "sugars." "Sugars" are those substances which are based on simple crystalline mono- and di-saccharide structures, *i.e.*, based on C<sub>5</sub> and C<sub>6</sub> sugar structures. They may include glucose, sucrose, fructose, lactose, maltose, pentose, arbinose, xylose, ribose, mannose, galactose, sorbose, dextrose and sugar alcohols, such as sorbitol, mannitol, xylitol, maltitol, isomalt, sucralose and the like and mixtures thereof. Sucrose is the preferred sugar.

Useful mixtures of carriers include the sugars listed above along with additional

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mono- di-, tri- and polysaccharides. Additional saccharides can be used in amounts of up to 50% by weight, preferably up to 30%, most preferably up to 20%, of the total carbohydrate content.

Optionally, the polysaccharides can be used alone as carriers. Polysaccharide carriers include polydextrose and the like. Polydextrose is a non-sucrose, essentially non-nutritive, carbohydrate substitute. It can be prepared through polymerization of glucose in the presence of polycarboxylic acid catalysts and polyols. Generally, polydextrose is commercially available in three forms: polydextrose A and polydextrose K, which are powdered solids; and polydextrose N supplied as a 70% solution. U.S. Patent No. 5,501,858 discusses polydextrose carriers.

If other carrier materials are used, they are employed in combination with sugar and not as total replacement therefor. For example, maltodextrins may be employed. Maltodextrins include mixtures of carbohydrates resulting from the hydrolysis of a saccharide. They are solids having a dextrose equivalent (DE) of up to and including 65. The carrier can also include maltooligo-saccharides produced by selective hydrolysis of corn starch. A general description of maltooligo-saccharides useful herein is set forth in co-owned U.S. Patent Nos. 5,347,431 and 5,429,836.

Applicants typically use the following systems of matrices, which systems are devoid of glycerine.

In the first system, xylitol is added to a mixture of saccharide-based carrier and one or more additional sugar alcohols, with sorbitol being favored as an added sugar alcohol. The carrier mix is flash-heat processed to provide a shearform floss having self-binding properties. Flosses made using sucrose, sorbitol and xylitol have been found to yield particularly effective self-binding properties. They exemplify "single floss" or "unifloss" systems.

The second system makes separate xylitol-containing binder flosses. The binder flosses ( binder portions ) are combined with base flosses ( base portions ), which contain a different sugar alcohol and a saccharide. Preferably, the base floss contains sorbitol and sucrose, while the binder floss contains xylitol and possibly sorbitol. These are termed "dual floss" systems.

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The ingredients which increase cohesiveness and lend self-binding properties preferably include sugar alcohols, such as sorbitol, xylitol, maltitol, mannitol and mixtures thereof, all of which form flosses. It is believed that the hygroscopic nature of these sugar alcohols increases the cohesiveness and self-binding character of matrices and matrix-containing formulations. Other sugar alcohols, especially hygroscopic ones, are contemplated.

Xylitol and sorbitol are the preferred sugar alcohols. Effective amounts of xylitol in the flosses are between about 0.5% and 25%, and preferably about 10% by weight. Sorbitol is used in the flosses in amounts of about 0.5% to about 40%.

10 When sorbitol and xylitol are used, the ratio of sorbitol to xylitol is from about 1:0.1 to about 1:10.

In dual floss systems, about 20 to about 80%, preferably about 34%, of the total floss content is xylitol-containing, or binder, floss. Likewise, the sorbitol-containing, or base, floss may be about 20 to 80 % of the total floss. In some "dual floss" embodiments, xylitol-containing flosses are first mixed with active ingredient(s), then mixed with sucrose/sorbitol flosses.

Regardless of the number of flosses, the total floss content preferably includes about 50 to about 85% sucrose, about 5 to about 20% sorbitol and about 5% to about 25% xylitol.

20 In some cases, flosses are used along with bio-affecting, or active, agents in the form of microsphere granulates or crystalline particles in the tableting process. It is preferred that the bio-affecting agent be coated as well. Often, a xylitol-containing floss is added to microspheres of one or more active agents first and then a non-xylitol-containing floss is added. Typically, the weight ratio of total floss to microspheres is about 1:1. In these instances, about 5% to about 25% of the floss is xylitol.

The amorphous shearform matrix of the present invention is preferably made from a feedstock which includes sucrose, sorbitol, and xylitol. As set forth in U.S.S.N. 08/915,068, filed August 20, 1997, these compositions have superior cohesiveness. In addition, the matrices, when partially recrystallized, yield matrix-containing mixes having particulate flowability such that they are suitable for use in high-speed and high-pressure



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tableting equipment to yield fast-dissolving tablets.

Applicants do not wish to be bound by a particular theory; however, they believe that a hygroscopic material must be present in the matrices and the matrices must be at least partially crystallized to provide good cohesiveness, self-binding properties and flow characteristics to the compositions containing them.

Applicants theorize that the hygroscopic material is initially present in the matrix in its amorphous state, but, due to its propensity to pick up moisture, it recrystallizes into a more crystalline structure. When sufficient recrystallization has occurred in the matrix as a whole, flowability is enhanced and the composition can be tableted on conventional tableting machines.

The compositions to be processed into comestible, or dosage, units generally contain conventional tableting additives. Conventional quantities of same may be incorporated into one or more of the matrices or may be mixed therewith prior to tableting. Useful amounts of conventional additives range from about 0.01% to about 80% by weight, based on the weight of the matrices or formulations in which they are used. The quantities may vary from these amounts, depending on the functions of the additives and the characteristics desired in the matrices and/or the final tablet compositions.

Conventional tableting aids and additives may be selected from a wide variety of materials such as lubricants, glidants, anti-caking agents and flow agents. For example, lubricants such as magnesium stearate, calcium stearate, sodium chloride, zinc stearate, hydrogenated vegetable oils, sterotex, polyoxyethylene, glyceryl monostearate, talc, polyethylene glycol, sodium benzoate, sodium lauryl sulfate, magnesium lauryl sulfate, sodium stearyl fumarate, adipic acid, light mineral oil and the like may be employed, with sodium stearyl fumarate preferred. Waxy fatty acid esters, such as glyceryl behenate, sold as "Compritol" products, can be used. Mixtures are operable.

Lubricants are used in amounts ranging from about 0% to about 10%, with about 0.01% to about 5.0% typically used.

Glidants such as starch, talc, lactose, stearates, dibasic calcium phosphate, magnesium carbonate, magnesium oxide, calcium silicate, Cabosil™ Syloid™ and silicon

dioxide aerogels may be employed.

Lactose, which may be a glidant or filler, can be added to the chopped floss at about 2% concentration to inhibit clumping. In some embodiments, the floss is chopped in the presence of lactose.

5           Glidants are present in amounts of about 0% to about 20%, with typical amounts being about 0.1% to about 5.0%.

The preformed matrices produced in accordance herewith are generally rendered partially crystalline, either alone or in the presence of additives, by one or more of the following crystallizing techniques.

10           The nature of the matrix feedstock determines whether the matrix is to be crystallized or recrystallized after it is formed. Highly amorphous feedstocks are crystallized. Crystalline ones are recrystallized. Nonetheless, the terms "crystallization" and "recrystallization" are used interchangeably in the following discussion.

15           The amorphous matrices are typically recrystallized by incorporating into, or contacting them with one or more crystallization promoters, termed "crystallization enhancers" and "crystallization modifiers." Both types of promoters assist in the recrystallization.

20           One technique for recrystallizing involves the use of crystallization enhancers. These are generally forces or physical materials that are used after the floss has been formed, but before the floss-containing composition is tableted. Suitable crystallization enhancers include ethanol, polyvinylpyrrolidone, water (*e.g.*, moisture), glycerine, radiant energy (*e.g.*, microwaves, heat, etc.) and the like. Combinations can be used. When recrystallization involves physical materials, as enhancers, typical amounts of these enhancers range from about 0.01% to about 10.0% by weight of the tablet composition.

25           Another crystallization technique involves crystallization modifiers. These crystallization modifiers are either (a) floss ingredients used at levels of about 0.01% to about 20.0% by weight of the floss, or (b) a combination of ingredients (a) with environmental agents or forces such as increased moisture and heat. The combination of additives with heat/humidity is called "aging."

30           Surfactants are preferred crystallization modifiers. Other materials which are non-

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saccharide hydrophilic organic materials may also be used. Useful modifiers preferably have a hydrophilic to lipid balance (HLB) of about 6 or more. Such materials include, without limitation, anionic, cationic, and zwitterionic surfactants as well as neutral materials with suitable HLB values. Hydrophilic materials having polyethylene oxide linkages are effective. Those with molecular weights of at least about 200, preferably at least 400, are highly useful.

Crystallization modifiers useful herein include: lecithin, polyethylene glycol (PEG), propylene glycol (PPG), dextrose, the SPANS and TWEENS which are commercially available from ICI America, and the surface active agents known as Carbowaxes. Generally, the polyoxyethylene sorbitan fatty acid esters called TWEENS, or combinations of such modifiers are used. Crystallization modifiers are usually incorporated into matrices in amounts of between about 0% and 10%.

Whether they are physical materials or forces, crystallization modifiers and/or enhancers are used at levels sufficient to give the floss/additive mixes the cohesivity and particular flowability needed for further processing, *e.g.*, molding into tablets.

The matrices are allowed to recrystallize, with or without added crystallization assistants, *i.e.*, modifiers and enhancers, either before or after they are combined with the non-matrix component(s), *e.g.*, the bio-affecting additives(s). The recrystallization level of the matrix generally reaches at least about 10% before tableting. Crystallization levels of 20% or more are highly effective. The use of partially recrystallized matrices leads to compositions that are free flowing and tabletable using conventional machines. U. S. Patent 5,597,416 describes a process for recrystallizing in the presence of additives.

Methods for effecting the recrystallization of the matrices include one or more of the following: use of Tween 80 or other crystallization modifier(s) in the matrix premix; aging of the matrix for up to several weeks; contacting the matrix with sufficient moisture and heat to induce crystallization; and treating the floss or the floss-containing composition with ethanol, ethanol vapors or another crystallization enhancer. Combinations of these may be used so that the matrices may be contacted with a crystallization enhancer while they are also in contact with moisture or heat.

When a surfactant, such as a Tween, is used, about 0.001% to about 1.00% is

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included in the floss preblend as a crystallization modifier. Following preblending, the formulations are processed into flosses, then chopped and used, with or without additives, to make tablets. Mixtures of surfactants can be used.

Aging may be used to recrystallize the matrix or floss. The aging process involves two steps. First the matrix, optionally containing at least one crystallization modifier, is formed, chopped and allowed to stand in closed or sealed containers without agitation under ambient conditions, *e.g.*, at room temperature and atmospheric pressure, for up to several days, preferably for about 1 to about 3 days. Later, the matrix is mixed, and optionally further chopped, with one or more other ingredients. The mix is then aged by allowing it to stand for an additional period of about 1 to about 3 days. Generally, the two-step aging process takes a total of about one week, with periods of about 4 to about 5 days being typical.

The flosses may also be recrystallized by subjecting them to increased heat and moisture without additives. This process is similar to aging, but involves shorter periods of time. Using a fluidized bed apparatus or other suitable agitating device, chopped floss is fluidized while heating, at ambient humidity and pressure, to a temperature of about 25°C to about 50°C. Generally, the temperature must be monitored to minimize clumping of floss particles. If any clumping occurs, the floss particles must be sieved before being further processed. Heating times of about 5 to about 30 minutes are typical.

When ethanol is used as a crystallization enhancer it is used in amounts, based upon the weight of the matrix, of about 0.1% to about 10%, with amounts of about 0.5% to about 8.0%, about 0.5% to about 7.0%, being very effective. The preformed matrix is contacted with ethanol. Excess ethanol is evaporated by drying for about 60 to 150 minutes at about 95°F to about 115°F, with 95°F to 105°F being highly useful. The drying step is carried out using tray drying, a jacketed mixer or other suitable method. Ethanol vapors may also be used. Following ethanol treatment, the matrix becomes partially. When the floss is partially recrystallized, it is granulated and tableted after blending with other ingredients. The tableting compositions flow readily and are cohesive.

When chewable products are made, it is preferred that partially crystalline ethanol-treated flosses be used. These flosses, often on optional lactose treatment (*i.e.*, chopping

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in the presence of lactose) are used in tabletable compositions.

U. S. Patent 5,610,076, incorporated herein by reference, discloses the use of ethanol to promote crystallization of surfactant-containing flosses.

Recrystallization of the matrix can be monitored by measuring the transmittance  
5 of polarized light therethrough or by the use of a scanning electron microscope. Amorphous floss or shearform matrix does not transmit polarized light and appears black in the light microscope when viewed with polarized light. Using bright field microscopy or the scanning electron microscope, the surface of the floss appears very smooth. In this condition, it is 0% recrystallized. That is, the floss is 100% amorphous.

10 Recrystallization of amorphous matrix starts at the surface of the mass and can be modified, *e.g.*, accelerated, by the presence of crystallization modifiers, as well as moisture. When Tweens assist the recrystallization, initiation of recrystallization is evidenced by a birefringence observed on the surface of the shearform matrix (floss) as viewed with polarized light. There are faint points of light riddled throughout the matrix surface. When  
15 birefringence appears, recrystallization has begun. At this stage, recrystallization is between about 1% and 5%.

As recrystallization proceeds, the birefringence on the surface of the matrix grows continually stronger and appears brighter. The points of light grow in size, number and intensity, seeming to almost connect. Using bright field or scanning electron microscopy,  
20 the surface of the matrix appears wrinkled. At this point, about 5 to 10% recrystallization has occurred.

When surfactants (*e.g.*, Tween 80) are mixed with matrix particles, droplets of surfactants become entrapped within the matrix particles. These droplets are obscured as recrystallization proceeds. As long as they are visible, the floss is generally not more than  
25 about 10% to 20% recrystallized. When they are no longer observable, the extent of recrystallization is no more than about 50%.

The recrystallization of the matrix results in reduction of the total volume of material. Ordered arrays of molecules take up less space than disordered arrays. Since recrystallization begins at the surface of the floss, a crust is formed which maintains the  
30 size and shape of the floss. There is an increase in the total free volume space within the

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floss as recrystallization nears completion, which manifests itself as a void inside the floss. This is evidenced by a darkened central cavity in light microscopy and a hollow interior in scanning electron microscopy. At this stage, the floss is believed to be about 50% to about 75% recrystallized.

5           The intensity of transmitted polarized light increases as the floss becomes more crystalline. The polarized light can be measured by a photon detector and assigned a value against calculated standards on a gray-scale.

          The final observable event in the recrystallization of floss is the appearance of fine, "cat whisker-like" needles and tiny blades which grow and project from the surface  
10 of the floss. These fine crystals, believed to be sorbitol (cat whiskers) and xylitol (blades), literally cover the floss like a blanket of fuzz. These features can be easily recognized by both light and electron microscopes. Their appearance indicates the final stage of recrystallization. The floss is now 100% recrystallized, *i.e.*, substantially non-amorphous.

15           The matrix portions of the tabletable composition are typically formed via flash-heat processing into a floss. The strands of the floss are macerated or chopped into rods for further processing. The rods of chopped floss have lengths of about 50 to about 500 microns.

          When active agents, such as bio-affecting agents, are added, they are often added  
20 in the form of particles, and generally as uniform coated microspheres. Suitable microspheres and other spheroidal particles can be made by "liquiflash" processes.

          "Liquiflash" processing involves the use of heat and pressure to reduce the feedstock to a condition in which resistance to flow, *e.g.*, viscosity, which impedes the propensity to form liquid droplets, is eliminated. In this condition, the mass has become  
25 liquid or liquiform." Once all resistance to flow is gone, shear force is applied to the feedstock until discrete particles separate from the mass. The particles, called "shearlite" particles, have a size and shape influenced only by natural mass separation of the flowing feedstock. U.S. Patent 5,458,823 and U.S. application SN. 08/330,412, filed October 28, 1994, both incorporated herein by reference, show processes and devices for such  
30 processing.

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The inventive compositions may include one or more active ingredients, such as bio-affecting agents. These are typically prescription or over the counter medications.

The active ingredients useful herein can be selected from a large group of therapeutic agents. Respective classes include those in the following therapeutic categories: ace-inhibitors; alkaloids; antacids; analgesics; anabolic agents; anti-anginal drugs; anti-allergy agents; anti-arrhythmia agents; antiasthmatics; antibiotics; anticholesterolemics; anticonvulsants; anticoagulants; antidepressants; antidiarrheal preparations; anti-emetics; antihistamines; antihypertensives; anti-infectives; anti-inflammatory; antilipid agents; antimanics; anti-migraine agents; antinauseants; antipsychotics; antistroke agents; antithyroid preparations; anabolic drugs; antiobesity agents; antiparasitics; antipsychotics; antipyretics; antispasmodics; antithrombotics; antitumor agents; antitussives; antiulcer agents; anti-uricemic agents; anxiolytic agents; appetite stimulants; appetite suppressants; beta-blocking agents; bronchodilators; cardiovascular agents; cerebral dilators; chelating agents; cholecystekinin antagonists; chemotherapeutic agents; cognition activators; contraceptives; coronary dilators; cough suppressants; decongestants; deodorants; dermatological agents; diabetes agents; diuretics; emollients; enzymes; erythropoietic drugs; expectorants; fertility agents; fungicides; gastrointestinal agents; growth regulators; hormone replacement agents; hyperglycemic agents; hypoglycemic agents; ion-exchange resins; laxatives; migraine treatments; mineral supplements; mucolytics, narcotics; neuroleptics; neuromuscular drugs; non-steroidal anti-inflammatories (NSAIDs); nutritional additives; peripheral vasodilators; polypeptides; prostaglandins; psychotropics; renin inhibitors; respiratory stimulants; sedatives; steroids; stimulants; sympatholytics; thyroid preparations; tranquilizers; uterine relaxants; vaginal preparations; vasoconstrictors; vasodilators; vertigo agents; vitamins; wound healing agents; and others.

Active agents which may be used in the invention include: acetaminophen; acetic acid; acetylsalicylic acid, including its buffered forms; acrivastine; albuterol and its sulfate; alcohol; alkaline phosphatase; allantoin; aloe; aluminum acetate, carbonate, chlorohydrate and hydroxide; alprozolam; amino acids; aminobenzoic acid; amoxicillin; ampicillin; amsacrine; amsalog; anethole; ascorbic acid; aspartame; astemizole; atenolol;

azatidine and its maleate; bacitracin; balsam peru; BCNU (carmustine); beclomethasone dipropionate; benzocaine; benzoic acid; benzophenones; benzoyl peroxide; benzquinamide and its hydrochloride; bethanechol; biotin; bisacodyl; bismuth subsalicylate; bornyl acetate; bromopheniramine and its maleate; buspirone; caffeine; 5 calamine; calcium carbonate, casinate and hydroxide; camphor; captopril; cascara sagrada; castor oil; cefaclor; cefadroxil; cephalixin; centriline and its hydrochloride; cetyl alcohol; cetylpyridinium chloride; chelated minerals; chloramphenicol; chlorcyclizine hydrochloride; chlorhexidine gluconate; chloroxylenol; chloropentostatin; chlorpheniramine and its maleates and tannates; chlorpromazine; cholestyramine resin; 10 choline bitartrate; chondrogenic stimulating protein; cimetidine and its hydrochloride; cinnamedrine hydrochloride; citalopram; citric acid; clarithromycin; clemastine and its fumarate; clonidine and its hydrochloride salt; clorifibrate; cocoa butter; cod liver oil; codeine and its fumarate and phosphate; cortisone acetate; ciprofloxacin HCl; cyanocobalamin; cyclizine hydrochloride; cyproheptadine and its hydrochloride; 15 danthron; dexbromopheniramine maleate; dextromethorphan and its hydrohalides; diazepam; dibucaine; dichloralphenazone; diclofen and its alkali metal sales; diclofenac sodium; digoxin; dihydroergotamine and its hydrogenates/mesylates; diltiazem; dimethicone; dioxybenzone; diphenhydramine and its citrate; diphenhydramine and its hydrochloride; divalproex and its alkali metal salts; docusate calcium, potassium, and 20 sodium; doxycycline hydrate; doxylamine succinate; dronabinol; efaroan; enalapril; enoxacin; ergotamine and its tartrate; erythromycin; estropipate; ethinyl estradiol; ephedrine; epinephrine bitartrate; erythropoietin; eucalyptol; famotidine; fenoprofen and its metal salts; ferrous fumarate, gluconate and sulfate; fluoxetine; folic acid; fosphenytoin; 5-fluorouracil (5-FU); fluoxetine and its hydrochloride; flurbiprofen; 25 furosemide; gabapentan; gentamicin; gemfibrozil; glipizide; glycerine; glyceryl stearate; granisetron and its hydrochloride; griseofulvin; growth hormone; guaifenesin; hexylresorcinol; hydrochlorothiazide; hydrocodone and its tartrates; hydrocortisone and its acetate; 8-hydroxyquinoline sulfate; hydroxyzine and its pamoate and hydrochloride salts; ibuprofen; indomethacin; inositol; insulin; iodine; ipecac; iron; isosorbide and its 30 mono- and dinitrates; isoxicam; ketamine; kaolin; ketoprofen; lactic acid; lanolin;



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lecithin; leuprolide acetate; lidocaine and its hydrochloride salt; lifinopril; liotrix;  
loratadine; lovastatin; luteinizing hormone; LHRH (luteinizing hormone replacement  
hormone); magnesium carbonate, hydroxide, salicylate, and trisilicate; meclizine and its  
hydrochloride; mefenamic acid; meclofenamic acid; meclofenamate sodium;  
5 medroxyprogesterone acetate; methenamine mandelate; menthol; meperidine  
hydrochloride; metaproterenol sulfate; methscopolamine and its nitrates; methsergide and  
its maleate; methyl nicotinate; methyl salicylate; methyl cellulose; methsuximide;  
metoclopramide and its halides/hydrates; metronidazole and its hydrochloride; metoprolol  
tartrate; miconazole nitrate; mineral oil; minoxidil; morphine; naproxen and its alkali  
10 metal sodium salts; nifedipine; neomycin sulfate; niacin; niacinamide; nicotine;  
nicotinamide; nimesulide; nitroglycerine; nonoxynol-9; norethindrone and its acetate;  
nystatin; octoxynol; octoxynol-9; octyl dimethyl PABA; octyl methoxycinnamate;  
omega-3 polyunsaturated fatty acids; omeprazole; ondansetron and its hydrochloride;  
oxolinic acid; oxybenzone; oxtriphylline; para-aminobenzoic acid (PABA); padimate-O;  
15 paramethadione; pentastatin; peppermint oil; pentaerythritol tetranitrate; pentobarbital  
sodium; perphenazine; phenelzine sulfate; phenindamine and its tartrate; pheniramine  
maleate; phenobarbital; phenol; phenolphthalein; phenylephrine and its tannates and  
hydrochlorides; phenylpropanolamine and its hydrochloride salt; phenytoin; pirlmenol;  
piroxicam and its salts; polymyxin B sulfate; potassium chloride and nitrate; prazepam;  
20 procainamide hydrochloride; procaterol; promethazine and its hydrochloride;  
propoxyphene and its hydrochloride and napsylate; pramiracetin; pramoxine and its  
hydrochloride salt; prochlorperazine and its maleate; propanolol and its hydrochloride;  
promethazine and its hydrochloride; propanolol; pseudoephedrine and its sulfates and  
hydrochlorides; pyridoxine; pyrolamine and its hydrochlorides and tannates; quinapril;  
25 quinidine gluconate and sulfate; quinestrol; ralitoline; ranitidine; resorcinol; riboflavin;  
salicylic acid; scopolamine; sesame oil; shark liver oil; simethicone; sodium bicarbonate,  
citrate, and fluoride; sodium monofluorophosphate; sucralfate; sulfanethoxazole;  
sulfasalazine; sulfur; sumatriptan and its succinate; tacrine and its hydrochloride;  
theophylline; terfenadine; thiethylperazine and its maleate; timolol and its maleate;  
30 thioperidone; tramadol; trimetrexate; triazolam; tretinoin; tetracycline hydrochloride;

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tolmetin; tolnaftate; triclosan; trimethobenzamide and its hydrochloride; tripeleennamine and its hydrochloride; tripolidine hydrochloride; undecylenic acid; vancomycin; verapamil HCl; vidaribine phosphate; vitamins A, B, C, D, B<sub>1</sub>, B<sub>2</sub>, B<sub>6</sub>, B<sub>12</sub>, E, and K; witch hazel; xylometazoline hydrochloride; zinc; zinc sulfate; zinc undecylenate.

- 5 Mixtures and pharmaceutically acceptable salts of these and other actives can be used.

Particularly useful active agents are sparingly soluble solid agents whose dissolution and release properties are enhanced by the solubilizing agents used herein.

- These agents include H<sub>2</sub> antagonists, analgesics, including non-steroidal anti-inflammatory drugs (NSAIDs), anticholesterolemics, anti-allergy agents, and anti-  
10 migraine agents.

Analgesics include aspirin, acetaminophen, acetaminophen plus caffeine, and non-steroidal anti-inflammatory drugs (NSAIDS), *e.g.*, ibuprofen and nimesulide.

- Useful NSAIDs include ibuprofen; diclofenac and its alkali metal salts; fenoprofen and its metal salts; flurbiprofen; ketoprofen; naproxen and its alkali metal salts;  
15 nimesulide; and piroxicam and its salts.

H<sub>2</sub>-antagonists which are contemplated for use in the present invention include cimetidine, ranitidine hydrochloride, famotidine, nizatidine, ebrotidine, mifentidine, roxatidine, pisatidine and aceroxatidine.

- Useful anti-allergy agents include hydricodone and its tartrates; clemastine and its  
20 fumarate; azatadine and its maleate; acetaminophen; hydroxyzine and its pamoate and hydrochloride salts; chlorpheniramine and its maleates and tannates; pseudoephedrine and its sulfates and hydrochlorides; bromopheniramine and its maleate; dextromethorphan and its hydrohalides; loratadine; phenylephrine and its tannates and hydrochlorides; methscopolamine and its nitrates; phenylpropanolamine and its hydrochlorides; codeine and its hydrochloride;  
25 codeine and its phosphate; terfenadine; acrivastine; astemizole; cetirizine and its hydrochloride; phenindamine and its tartrate; tripeleennamine and its hydrochloride; cyproheptadine and its hydrochloride; promethazine and its hydrochloride; and pyrilamine and its hydrochlorides and tannates.

- Useful antimigraine agents include divalproex and its alkali metal salts; timolol  
30 and its maleate; propranolol and its hydrohalides; ergotamine and its tartrate; caffeine;

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sumatriptan and its succinate; dihydroergotamine, its hydrogenates/mesylates; methsergide and its maleate; isometheptene mucate; and dichloralphenazone.

Another class of drugs which can be used are antiemetics. Useful antiemetics include: meclizine and its hydrochloride; hydroxyzine and its hydrochloride and  
5 pamoate; diphenhydramine and its hydrochloride; prochlorperazine and its maleate; benzquinamide and its hydrochloride; granisetron and its hydrochloride; dronabinol; bismuth subsalicylate; promethazine and its hydrochloride; metoclopramide and its halides/hydrates; chlorpromazine; trimethobenzamide and its hydrochloride; thiethylperazine and its maleate; scopolamine; perphenazine; and ondansetron and its  
10 hydrochloride.

Other active ingredients for use in the present invention include antidiarrheals such as Imodium AD, antihistamines, antitussives, decongestants, vitamins, and breath fresheners. Also contemplated for use herein are anxiolytics such as Xanax; antipsychotics such as Clozaril and Haldon; antihistamines such as Seldane, Hismanal,  
15 Relafen, and Tavist; antiemetics such as Kytril and Cesamet; bronchodilators such as Bentolin, Proventil; antidepressants such as Prozac, Zoloft, and Paxil; antimigranes such as Imigran, ACE-inhibitors such as Vasotec, Capoten and Zestril; Anti-Alzheimers agents such as Nicergoline; and  $\text{Ca}^{II}$ -Antagonists such as Procardia, Adalat, and Calan.

Among the anticholesterolemics, the statins, *e.g.*, lovastatin, provastatin and the  
20 like, are notable.

Combinations of various types of drugs, as well as combinations of individual drugs, are contemplated.

One group of preferred active ingredients are antacids,  $\text{H}_2$ -antagonists and analgesics.

25 Antacid dosages can be prepared using ingredients such as: aluminum hydroxide, dihydroxyaluminum aminoacetate, aminoacetic acid, aluminum phosphate, dihydroxyaluminum sodium carbonate, bicarbonate, bismuth aluminate, bismuth carbonate, bismuth subcarbonate, bismuth subgallate, bismuth subnitrate, calcium carbonate, calcium phosphate, citrate ion (acid or salt), amino acetic acid, hydrate of  
30 magnesium aluminum sulfate, magaldrate, magnesium aluminosilicate, magnesium

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carbonate, magnesium glycinate, magnesium hydroxide, magnesium oxide, magnesium trisilicate, milk solids, aluminum mono- or di-basic calcium phosphate, tricalcium phosphate, potassium bicarbonate, sodium tartrate, sodium bicarbonate, magnesium aluminosilicates, tartaric acids and salts, and the like. Mixtures are operable. Moreover,  
5 antacids can be used in combination with H<sub>2</sub>-antagonists.

Chewable antacid compositions which dissolve quickly can be made using the compositions of the invention.

Preferred analgesics include aspirin, acetaminophen, acetaminophen plus caffeine, and ibuprofen.

10 Other useful active ingredients include antidiarrheals such as IMMODIUM AD; antihistamines; antitussives; decongestants; vitamins and breath fresheners. Also contemplated are anxiolytics such as XANAX; antipsychotics such as CLOZARIL and HALDOL; non-steroidal antiinflammatories, such as VOLTAREN AND LODINE; antihistamines such as SELDANE, HISMANAL, RELAFEN and TAVIST; antiemetics  
15 such as KYTRIL and CESAMET; bronchodilators such as BENTOLIN, PROVENTIL; antidepressants such as PROZAC, ZOLOFT, and PAXIL; antimigraine agents such as IMIGRAN; ace-inhibitors such as VASOTEC, CAPOTEN AND ZESTRIL; anti-Alzheimers agents such as NICERGOLINE; and Ca<sup>++</sup>-antagonists such as PROCARDIA, ADALAT and CALAN.

20 H<sub>2</sub>-antagonists contemplated include cimetidine, ranitidine hydrochloride, famotidine, nizatidine, ebrotidine, mefentidine, roxatidine, pisatidine and aceroxatidine.

Other ingredients which may be included are fillers, fragrances, dyes, flavors, sweeteners (both artificial and natural), and other conventional tablet additives.

For example, fillers may be used to increase the bulk of the tablet. Some useful  
25 fillers include calcium sulfate, both di- and tri-basic; starch; calcium carbonate; microcrystalline cellulose; modified starches, lactose, sucrose; mannitol and sorbitol.

Flavors may be chosen from natural and synthetic flavoring liquids. An illustrative list of such agents includes volatile oils, synthetic flavor oils, flavoring aromatics, oils, liquids, oleoresins and extracts derived from plants, leaves, flowers, fruits,  
30 stems and combinations thereof. A non-limiting representative list of these includes citric

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oils, such a lemon, orange, grape, lime and grapefruit an fruit essences, including apple, pear, peach, grape, strawberry, raspberry, cherry, plum, pineapple, apricot, or other fruit flavors.

Other useful flavorings include aldehydes and esters, such as benzaldehyde  
5 (cherry, almond); citral, i.e., alpha-citral (lemon, lime); neral, i.e., beta-citral (lemon, lime); decanal (orange, lemon); aldehyde C-8 (citrus fruits); aldehyde C-9 (citrus fruits); aldehyde C-12 (citrus fruits); tolyl aldehyde (cherry, almond); 2,6-dimethyloctanal (green fruit); 2-dodedenal (citrus, mandarin); mixtures thereof and the like.

The sweeteners may be chosen from the following non-limiting list: glucose (corn  
10 syrup), dextrose, invert sugar, fructose, and mixtures thereof (when not used as a carrier); saccharin and its various salts, such as the sodium salt; dipeptide sweeteners such as aspartame; dihydrochalcone compounds, glycyrrhizin; Stevia Rebaudiana (Stevioside); chloro derivatives or sucrose such as sucralose; and sugar alcohols such as sorbitol, mannitol, xylitol, and the like. Also contemplated are hydrogenated starch hydrolysates  
15 and the synthetic sweeteners such as 3,6-dihydro-6-methyl-1-1-1,2,3-oxathiazin-4-one-2,2-dioxide, particularly the potassium salt (acesulfame-K), and sodium and calcium salts thereof. Other sweeteners may also be used.

Some embodiments include one or more effervescent disintegration agents to aid in masking the objectionable taste of active ingredients, such as vitamins, medicines  
20 and/or minerals, etc. The positive organoleptic sensation achieved by the effervescent action in the mouth, as well as the texture, speed and sensation of disintegration, aid in masking undesirable flavors.

"Effervescent" refers to those agents which evolve gas. The gas- or bubble-generating action is often the result of the reaction of a soluble acid source and a  
25 carbonate source. The reaction of these two general classes of compounds produces carbon dioxide gas upon contact with water in saliva. Useful acids include: citric, tartaric, malic, fumaric, adipic, succinic and acid salts and anhydrides thereof. Acid salts may also include sodium dihydrogen phosphate, disodium dihydrogen pyrophosphate, acid citrate salts and sodium acid sulfite. While the food acids can be those indicated above, acid  
30 anhydrides of the above-described acids may also be used. Carbonate sources include dry

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solid carbonate and bicarbonate salts such as sodium bicarbonate, sodium carbonate, potassium bicarbonate and potassium carbonate, magnesium carbonate and sodium sesquicarbonate, sodium glycine carbonate, L-lysine carbonate, arginine carbonate and amorphous calcium carbonate. Mixtures of various acid and carbonate sources, as well as  
5 other sources of effervescence, can be used.

The effervescent agent can be included in at least three different ways. The first method includes incorporating the entire effervescent agent in the feedstock which is used to form the shearform product. The second involves adding the agent to an already formed shearform matrix. The third method incorporates one portion of the agent in the  
10 shearform matrix and adds another portion after formation of the matrix material. The artisan can determine the best way to use the agent for its effervescent properties.

Other ingredients include binders which contribute to the ease of formation and general quality of the tablet. Binders include starches, pregelatinized starches, gelatin, polyvinylpyrrolidone, methylcellulose, sodium carboxymethylcellulose, ethylcellulose,  
15 polyacrylamides, polyvinylloxazolidone and polyvinylalcohols.

Color additives can be used in preparing tablets. Such color additives include food, drug and cosmetic colors (FD&C), drug and cosmetic colors (D&C) or external drug and cosmetic colors (Ext. D&C). These colors are dyes, lakes, and certain natural and derived colorants. Useful lakes include dyes absorbed on aluminum hydroxide or  
20 other suitable carriers.

An optional feature involves microspheres which are components of substrate/coating systems. The substrate can be a non-active ingredient, such as a saccharide-based material, or it can be an active or a combination of actives. In one embodiment, the substrates are sugar shearlite particles having active agents coated  
25 thereon. The coating may include other types of coating materials, *e.g.*, coloring agents. Additional coatings can be used.

Other useful substrate/coating systems employ substrates which are shearlite particles of one or more actives. Coatings thereon can contain saccharides and other ingredients.

30 Controlled release coatings, *e.g.*, sustained release coatings, are among the

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preferred types of coatings for use in dosage forms which include bio-affecting agents.

Using the invention, strong, highly attractive dosage units, *e.g.*, tablets, can be produced having textures and internal structures which are relatively open to solubilization. Applicants' compositions are intended generally formed into tablets at pressures of from about 500 up to about 6,000 psi.

When chewable comestible units are made, they are typically compressed to hardnesses of about 3 to about 15 SCU's, preferably about 4 to about 6. Tablet thicknesses for chewables are about 0.2 to about 0.3 inches.

The following non-limiting examples illustrate the invention.

10

### EXAMPLE I

#### Ibuprofen Microspheres

Ibuprofen was processed into spheres as follows:

An ibuprofen powder feedstock was fed to the 5-inch spinning head disclosed in U. S. Patent Application Serial No. 08/874,215 filed on June 13, 1997, entitled A SPINNER HEAD HAVING FLOW RESTRICTING INSERTS. The head was rotated at about 3600 rpm while the heating elements were raised to a temperature which produced the liquiflash conditions. The feedstock also contained 10% Compritol 888 ATO and 2% Gelucire 50/13. (Compritol 888 ATO is glycerol behenate NF, a lipophilic additive from Gattefosse S.A., a French company. Gelucire, a polyethylene glycol 32 glyceryl ester solubility enhancer, is also available from Gattefosse.)

The spinning head forced the material through the screen and the product was permitted to free fall a distance of from 6 to 8 feet below the head. The product consists of spheres having a highly consistent particle size, with diameters ranging from about 50 to 200 microns.

The product was subjected to testing to determine the time required for dissolution of the active ingredient. The monograph is provided by the U.S. Pharmacopeial Convention, Inc. In the U.S. Pharmacopoeial National Formulary Monograph for Ibuprofen Dissolution Study, U.S. 23 NF 18, page 786 (1995). At a composition level of 88% ibuprofen, the time for dissolution of most of the ibuprofen was about 15 minutes. Virtually total dissolution occurred at around 20 to 25 minutes. These results show high

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predictability for delivery using these microspheres.

The microspheres can be coated with taste masking coatings containing ethyl acrylate and methyl methacrylate polymers and hydroxypropyl methylcellulose polymers.

### EXAMPLE II

#### 5                    Acetaminophen Microspheres

Acetaminophen powder (melting point 169-170.5°C) was made into microspheres using a procedure similar to that described in Example I. Fine spheres, all smaller than about 420 microns in diameter, were formed. The spheres were coated with ethyl cellulose polymers and hydroxypropyl cellulose polymers for taste masking.

#### 10                   EXAMPLE III

#### Unifloss

Using a procedure similar to that of Example I, ibuprofen (IBP) microspheres were made from a formulation containing 88% ibuprofen, 10% Compritol and 2% Gelucire.

15                   A preblend of 78.25% sucrose, 11.0% sorbitol, 10.0% xylitol and 0.75% TWEEN 80 was prepared.

The Floss preblend was processed using the 5" crown head disclosed in U.S.S.N. 08/854,344, filed May 12, 1997, at a temperature of 250° C and rotational speed of 60Hz (3600rpm). The floss collected was chopped in the Littleford FKM600 mixer with 2% lactose (2%w/w of the floss) for 2 minutes at 100rpm with the choppers on. 200 proof  
20                   ethanol (0.5% based on weight of the floss) was sprayed on the chopped floss and mixed. The floss was then dried at 40-45° C for 60-90 minutes with intermittent mixing. The dried floss was screened through a 20 mesh screen.

The microspheres and floss were then admixed used in the following composition:

	<u>Composition</u>	<u>Percentage</u>
25	IBP Microspheres	34.4
	Floss	62.7
	Citric Acid	0.7
	Lemon Flavor	0.4
	Whipped Cream Flavor	0.3
30	SYLOID 244 FP	0.5
	Sodium Stearyl Fumarate	1.0

The screened floss was blended with ibuprofen microspheres in the Littleford



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mixer for 5 minutes. To this mix, flavors and flow agent were added and blended for another 2 minutes. Lastly, the lubricant (sodium stearyl fumarate) was added and blended for another 2 minutes. The blend was then tableted on a Kilian T200 rotary tablet press using 15mm round flat-faced radial edge punches. The tablet weight was maintained at 750mg and the hardness was maintained between 1.0 and 4.0 lb.

#### **EXAMPLE IV**

##### **Reduced Xylitol Floss**

Using the procedure of Example I, ibuprofen microspheres were made from a formulation containing 88% ibuprofen, 10% Compritol and 2% Gelucire. Via a single floss process similar to that of Example VI, a floss was made from the following composition: 83.25% sucrose, 11.0% sorbitol, 5.0% xylitol and 0.75% TWEEN.

The microspheres and floss were used in the following composition:

	<u>Composition</u>	<u>Percentage</u>
	IBP Microspheres	34.4
15	Floss	62.7
	Citric Acid	0.7
	Lemon Flavor	0.4
	Whipped Cream Flavor	0.3
	SYLOID 244 FP	0.5
20	Sodium Stearyl Fumarate	1.0

The ingredients were mixed and the mix was tableted using procedures as described in Example III.

#### **EXAMPLE V**

##### **Acetaminophen Tablets**

Using a procedure similar to that employed in Example I, acetaminophen (APAP) microspheres were made from a formulation containing 90% APAP, 7.5% carnauba wax, and 2.5% Pluronic F68. The spheres were then coated with a 45:55 mixture of ethyl cellulose and hydroxypropyl cellulose.

Using the procedure shown in Example III, a unifloss was made containing 78.25% sucrose, 11.00% sorbitol, 10.00% xylitol and 0.75% Tween 80. The floss was chopped in the presence of 2% lactose and granulated after the addition of 0.5% ethanol.

Tablets were made from the following composition:

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	<u>Composition</u>	<u>Percentage</u>
	APAP Microspheres	46.22
	Floss	48.68
	Grape Flavor	0.70
5	Citric Acid	0.30
	Mannitol	2.00
	SYLOID	0.10
	Adipic Acid	2.00

Using a Kilian T200 press, 500 mg tablets were pressed to a 2 lb. initial hardness  
 10 (compaction pressures up to 8000 psi) by placing the composition in the feed hopper and  
 allowing gravity to feed the dies.

#### EXAMPLE VI

##### Cimetidine Tablets

Using procedures set out in Example V, microspheres were made from the  
 15 following composition:

	<u>Composition</u>	<u>Percentage</u>
	Cimetidine	40
	Myvaplex 600	50
	Pluronic F68	10

20 The microspheres were coated for taste masking with a coating containing ethyl  
 cellulose and hydroxypropylcellulose.

Using a procedure similar to that of Example I, a floss was made from the  
 following composition:

	<u>Ingredient</u>	<u>Percentage</u>
25	Sucrose	83.25
	Sorbitol	11.00
	Xylitol	5.00

Later, the following formulation was mixed and tableted:

	<u>Ingredient</u>	<u>Percentage</u>
30	Cimetidine Beads	33.90
	Floss	63.80
	Lemon Flavor	0.60
	Aspartame	0.60
	Citric Acid	1.00
35	SYLOID	0.10

Using a Kilian T200 press, 750 mg tablets were pressed to a 2 lb. initial hardness.

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**EXAMPLES VIIa and VIIb****Vitamin C Tablets****Example VIIa**

A floss containing 78.25% sucrose, 11.00% sorbitol, 10.0% xylitol and 0.75%

5 Tween 80 was prepared as follows:

The mix of ingredients (2kg) was spun into floss at 3600rpm (60Hz) using a 5" spinning head in the device described in U.S. Serial No. 08/854,344, filed May 12, 1997.

The floss was chopped in a high shear mixer/chopper for 2 minutes.

The floss was treated with 0.5% ethanol and allowed to dry for 90 minutes.

10 The ethanol-treated floss particles were then used in the following formulation:

	<u>Component</u>	<u>Weight (%)</u>
	DESCOTE 60% Ascorbic Acid	30.77
	Floss	63.00
	Milled Adipic Acid	2.00
15	Mannitol	3.00
	Natural Orange Flavor	1.00
	SYLOID FP244	0.10
	FD&C Yellow #6 Lake	0.10
	MAGNASWEET 100	0.03
20	TOTAL	100.00

The ingredients were mixed in a Littleford Mixer for 10 to 15 minutes. The mix was tableted on a Kilian T-200 press to yield 0.65g tablets containing 120mg vitamin C of 2 pounds hardness, and 3.06% moisture content, having thicknesses of 4.5mm to 5.5mm.

**Example VIIb**

25 Using the floss particles and the general procedure of Example 1, 250mg tablets of ascorbic acid, weighing 1 gram each, were made from the following formulation:

	<u>Component</u>	<u>Weight (%)</u>
	DESCOTE 60% Ascorbic Acid	43.75
	Floss	50.20
30	Citric Acid	0.70
	Mannitol	3.00
	Natural Orange Flavor	1.50

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SYLOID FP244	0.25
FD&C Yellow #6 Lake	0.10
Sodium stearyl fumarate	0.50
TOTAL	100.00

5        Organoleptic tests, used to indicate dissolution, showed that the tablets of Examples a and b dissolved in the mouth, without chewing or drinking water, in 5 to 10 seconds.

### EXAMPLE VIII

For a 500mg chewable tablet of ascorbic acid, (Vitamin C), the floss was  
 10 prepared and chopped using the general procedure of Example VII. The chopped floss was treated with 4.0% ethanol and allowed to dry for 90 minutes. The 4.0% ethanol-treated floss particles were then used in the following formulation.

<u>Composition</u>	<u>Weight (%)</u>
DESCOTE 60% Ascorbic Acid	50.00
15 Floss (4% ethanol-treated)	43.25
Mannitol	3.00
Natural Orange Flavor	1.50
SYLOID 244FP	0.50
Magnesium Stearate	1.50
20 Color	0.25

The ingredients were mixed in a Littleford Mixer for 10 to 20 minutes. The mix was tableted on a Kilian T-200 press to yield 1.75g tablets of 11 pounds hardness, having a thickness of 6.5 to 7.5mm.

### EXAMPLE IXA

25        A chewable calcium carbonate/Vitamin D product was made as follows:

<u>Floss Formulation</u>	<u>Percentage</u>
Sucrose	78.25
Sorbitol	11.00
Xylitol	10.00
30 Polysorbate 80	0.75

The sucrose, sorbitol, xylitol, and Polysorbate 80 were blended in a Littleford FKM600 mixer for 10 minutes. The blend was then subjected to Shearform process at 60HZ and 250° C temperature using the 5" crown head described in U.S.S.N. 08/854,344, filed May 12, 1997. The floss manufactured was chopped in the Littleford FKM600  
 35 mixer with 2% lactose and treated with ethanol (7% of the floss). The floss was dried at

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45°C for 150 minutes. The floss was then milled/sieved through a 20 mesh screen using a Fitzmill or Apexmill.

	<u>Tablet Formulation</u>	<u>Percentage</u>
5	Calcium Carbonate Destab SE 95%	47.85
	Vitamin D <sub>3</sub>	0.16
	Floss	48.48
	N&A Lemon Flavor	1.00
	Citric Acid	1.00
10	SYLOID 244 FP	0.50
	Magnesium Stearate	1.00
	The calcium carbonate was blended with Vitamin D <sub>3</sub> for 15 minutes at speed 1 in a Diosna 600. The milled floss was added and blended further for 10 minutes. The flavors and flow agent was added and blended for additional 3 minutes. The magnesium stearate was added and blended for additional 7 minutes. The blend was compressed on a	
15	rotary tablet press at 85N hardness, 2.75g tablet weight, 19mm concave round or 19mm flat-faced radial edge tooling.	

#### Example IX B

The floss from example IX A was used in the following formulation to make 550 my CaCO<sub>3</sub> EX Chew tablets.:

	<u>Tablet Formulation</u>	<u>Percentage</u>
20	Calcium Carbonate Destab SE 95%	38.60
	Floss	56.40
	Artificial Cherry Flavor	0.50
	Mannitol Powder	3.00
25	SYLOID 244 FP	0.50
	Magnesium Stearate	<u>1.00</u>
		100%

The calcium carbonate was blended with floss for 10 minutes in a Littleford FKM 600 mixer. The flavor and mannitol was added and blended further for 3 minutes. The flow agent was added and blended for additional 3 minutes. The magnesium stearate was added and blended for an additional 4 minutes. The blend was compressed on a Kilian rotary tablet press to 100-120 N hardness, 1.5g tablet weight, using 16.5mm flat faced radial edge tooling.

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**Example X**

Chewable ibuprofen tablets were made from the following formulations:

Floss Formulation:

	<u>Ingredient</u>	<u>% in Formulation</u>
5	Sucrose	84.5
	Mannitol	5.0
	Sorbitol	5.0
	Xylitol	5.0
	Polysorbate 80	0.5
10	The floss preblend was processed using the 5" crown head disclosed in U.S.S.N. 08/854,344, filed May 12, 1997, at a temperature of 183°C and rotational speed of 60HZ (3600rpm). The floss collected was chopped in the Stephan mixer for 1-2 minutes at "hi" speed setting. 200 proof ethanol (4% of the formulation) was sprayed on the chopped floss with simultaneous mixing in a Hobart planetary mixer. The floss was then placed in	
15	flat trays and dried at 35-40°C for 60-90 minutes with intermittent agitation in an oven. The dried floss was screened through a 20 mesh screen using a Quadro Comil.	

The dry granulation was mixed with tablet excipients, as follows:

Tablet Formulation:

	<u>Ingredient</u>	<u>% in Formulation</u>
20	Ibuprofen taste masked microspheres	23.1
	Floss matrix	64.5
	Aspartame	0.8
	Magna Sweet 100	0.25
	Flavor	0.9
25	Citric Acid (anhydrous)	0.9
	Adipic Acid	0.7
	Miragel 463 Starch	2.0
	Mannitol	5.0
	Syloid 244FP	0.75
30	Magnesium Stearate	1.0
	Color	0.1

The floss preblend was processed using the 5" crown head disclosed in U.S.S.N. 08/854,344, filed May 12, 1997, at a temperature of 183°C and rotational speed of 60HZ (3600rpm). The floss collected was chopped in the Stephan mixer for 1-2 minutes at "hi" speed setting. 200 proof ethanol (4% of the formulation) was sprayed on the chopped

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floss with simultaneous mixing in a Hobart planetary mixer. The floss was then placed in flat trays and dried at 35-40° C for 60-90 minutes with intermittent agitation. The floss was screened through a 20 mesh screen using a Quadro comil. The screened floss was blended with ibuprofen microspheres in the Hobart planetary mixer for 3-5 minutes.

- 5 Flavors and flow agents were added and blended for another 2-4 minutes. Lastly, the lubricant (magnesium stearate) was added and blended for an additional 2 minutes.

The blend was then tabletted on a Stokes rotary tablet press using round flat-faced beveled edge tooling to give tablets having varying weights, as follows: The punch size was 5/8" for 200mg ibuprofen equivalent tablets (1.2g tablets), 1/2" for 100mg ibuprofen  
10 equivalent tablets (0.6g tablets), and 3/8" for 50mg ibuprofen equivalent tablets (0.3g tablets). The hardness of the tablets was maintained between 3.0 and 7.0 SCU.

The following table shows quantity ranges in which various ingredients can be used to make chewable ibuprofen tablets via procedures such as those described above.

	<u>Ingredient</u>	<u>% in Formulation</u>
15	Ibuprofen taste masked microspheres	20.0-25.0
	Floss matrix	55.0-65.0
	Aspartame	1.3
	Magna Sweet 100	1.5
	Flavor	0.8-1.0
20	Citric Acid Anhydrous	0.4-0.9
	Adipic Acid	0.5-1.0
	Miragel 463 Starch	2.0
	Mannitol	5.0
	Syloid 244FP	0.75
25	Magnesium Stearate	1.0
	Color	0.1

Reasonable variations, such as those which would occur to a skilled artisan, can be made herein without departing from the scope of the invention.

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**We claim:**

1. A process for preparing fast dissolving comestible units comprising the steps:
  - 5 (1) providing amorphous shearform particles,
  - (2) treating the particles of (1) with at least one material selected from the group consisting of: ethanol and lactose,
  - (3) blending optionally coated particles containing at least one bio-affecting agent with the treated shearform particles,
  - 10 (4) shaping and compressing the blend to produce comestible units.
2. The process of Claim 1 wherein the bio-affecting agent is in the form of microspheres.
- 15 3. A chewable tablet made via the process of Claim 1.
4. A flowable composition for making comestible units comprising:
  - a) partially crystallized shearform particles treated with at least one of ethanol and lactose, and
  - 20 b) optionally coated particles containing at least one bio-affecting agent.
5. The composition of Claim 1 wherein the particles have been pretreated with lactose.
- 25 6. The composition of Claim 2 wherein (b) contains at least one agent selected from the group consisting of: analgesics, antacids and vitamins.
7. The composition of Claim 3 wherein (b) is in the form of microspheres.
- 30 8. The composition of Claim 2 wherein both ethanol and lactose are used to



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produce (a).

9. The composition of Claim 5 wherein (b) contains at least one agent selected from the group consisting of: analgesics, antacids and vitamins.
- 5
10. The composition of Claim 6 wherein (b) is in the form of microspheres.

# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/US 98/16520

<b>A. CLASSIFICATION OF SUBJECT MATTER</b> IPC 6    A61K9/00    A61K9/20		
According to International Patent Classification (IPC) or to both national classification and IPC		
<b>B. FIELDS SEARCHED</b> Minimum documentation searched (classification system followed by classification symbols) IPC 6    A61K		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practical, search terms used)		
<b>C. DOCUMENTS CONSIDERED TO BE RELEVANT</b>		
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 711 547 A (FUISZ TECHNOLOGIES LTD) 15 May 1996 see column 4, line 38 - column 5, line 3 see column 6, line 53 - column 7, line 10 see column 7, line 22-31 see column 14, line 40-42 see column 15, line 16-39 see column 18, line 19-31 see claims 30,33 <div style="text-align: center; margin-top: 20px;">--- -/--</div>	1,3,4
<div style="display: flex; justify-content: space-between;"> <span><input checked="" type="checkbox"/> Further documents are listed in the continuation of box C.</span> <span><input checked="" type="checkbox"/> Patent family members are listed in annex.</span> </div>		
<b>* Special categories of cited documents :</b>		
<div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 45%;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&amp;" document member of the same patent family</p> </div> </div>		
Date of the actual completion of the international search  <div style="text-align: center; font-weight: bold;">7 December 1998</div>		Date of mailing of the international search report  <div style="text-align: center; font-weight: bold;">15/12/1998</div>
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016		Authorized officer  <div style="text-align: center; font-weight: bold;">La Gaetana, R</div>

# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/US 98/16520

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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X	<p>US 5 587 172 A (MYERS GARRY L ET AL)  24 December 1996  cited in the application  see column 3, line 43-55  see column 4, line 6-14  see column 4, line 21-23  see column 8, line 6-11  see column 8, line 29-49  see column 11, line 53 - column 12, line 9  see claims 1-3,8</p> <p style="text-align: center;">----</p>	1,3,4
A	<p>US 5 601 076 A (BATTIST GERALD ET AL)  11 February 1997  cited in the application  see column 4, line 45-50  see column 5, line 11-20  see column 5, line 32-37  see column 9, line 9-39  see column 11, line 30 - column 12, line 57  see column 16, line 51 - column 17, line 5  see claims 1,5-7,9</p> <p style="text-align: center;">-----</p>	1-10

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